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Blood pressure and dementia

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Hypertension has proven to be a major predisposing factor for the development of both vascular and degenerative (Alzheimer's) dementias, either following stroke or gradually through more insidious microcerebrovascular processes. In the latter case the interval between the respective manifestations of hypertension and dementia may vary between a few years and several decades. The temporal relationships may become complicated by the finding that blood pressure tends to fall shortly before the onset of overt Alzheimers' disease. Whether or not timely antihypertensive regimens may delay or even prevent the development of dementias later in life is still an "educated" guess, as long there has been no comprehensive trial comparing the potential of the different antihypertensive drug classes in this regard. Until then, the class of dihydropyridine calcium antagonists (exemplified by nitrendipine in the Syst-Eur trial) is the only category having statistically been proven to be of substantial value for prevention of Alzheimer's disease.

KEY WORDS: Hypertension - Alzheimer's disease - Vascular dementia - Antihypertensive agents - Dementia, prevention and control.

Cognitive deterioration and its climactic end point, overt dementia, may briefly be defined in terms of: progressive memory loss, disorientation in time and space, loss of autonomy, and worst of all depersonalisation/alienation.

The dementia syndrome, in terms of clinical background and morphological cerebral substrates, traditionally used to be specified into 2 main prototypes: degenerative dementia or Alzheimer's disease, *versus* vascular dementia. Despite a vast and ongoing literature on differential features between the 2 forms, probably including genetic markers, the overruling importance of such discriminating characteristics is now fading away in the face of integrated epidemiologically-oriented research. Hofman and his group in Rotterdam [1] have shown that the 2 subtypes share atherosclerosis as a major background factor (Figure 1).[1]

This subsequently has given rise to interesting and far-reaching theoretical considerations, which however failed to take into account the potentially dominant role of hypertension as one major common denominator in both disease variants.[2] An authoritative collaborative neuropathological study under the auspices of the Medical Research Council in the UK also arrived at the conclusion that there is a considerable overlap between the microscopical substrates of degenerative and vascular dementia, such as the occurrence of neurofibrillary tangles.[3]

The causative role of hypertension in both dementia types will be documented further on.

Epidemiology of dementias at large

Both subtypes of dementia are associated with the aging process and hence increase *pari passu* with the longevity of mankind, as estimated in the Europe and the USA In the Western World, some 10 years ago the prevalence of memory impairment in the older population was already estimated to be 17-34%,[4-7] and overt

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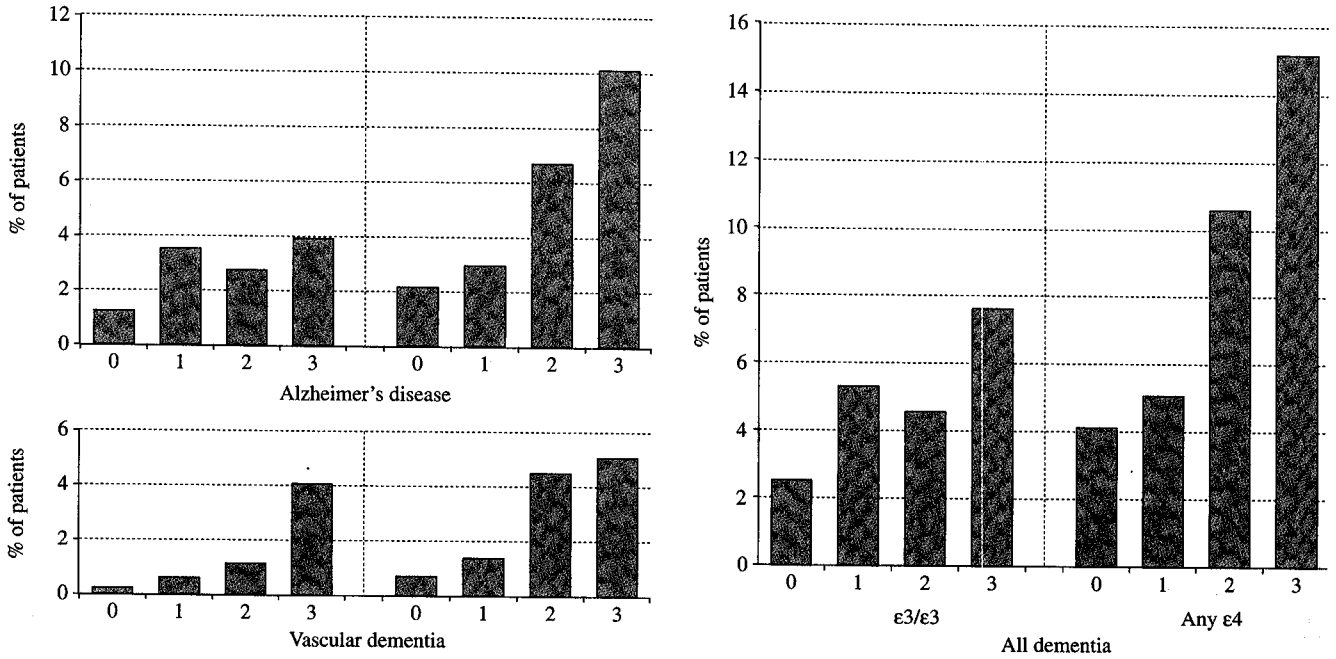

Figure 1.—Proportions of patients with A) Alzheimer's disease, vascular dementia, and B) all dementias adjusted for age and sex, by apolipoprotein-E genotype and atherosclerosis score. [Modified from Hofman *et al.*[1]].

Aging
Family history
Apolipoprotein E e 4 allele
Sex (female>male)
Vascular risk factors & damage (hypertension*, diabetes, stroke)
Depression
Poor education level
Sedentary life style
Social disengagement

* Variability of blood pressure?

Figure 2.—Factors involved in cognitive impairment and dementias.

dementia (80% of the Alzheimer type) affected 3.6-10.3% of the population over the age of 65 years.[8, 9]

In the U.S.A. alone, again 10 years ago, roughly 4 million elderly were already victimized by Alzheimers' disease.[9]

It is estimated that the incidence of dementia exponentially increases with age with rates of 5-10 cases per 1 000 person years at 70 years up to 20-40 cases per 1 000 at 80 years.[10] Hence, given the current worldwide demographic transition from high to low rates of birth and death, dementia is bound to grow into one of the principal causes of disability and reduced general quality of life in the community at large. In the U.S.A., the prevalence of Alzheimer's disease will quadruple over the next 50 years.[11] The major concern is that medical treatment of established dementia so far has shown only marginal benefit, without any promise of cost-effectiveness.[11, 12]

This reinforces the need for focusing on the possibility of prophylactic measures, to be derived from potential co-factors involved in the pathogenesis of degenerative and vascular dementias. Unfortunately most of those are hardly, if at all, amenable to social or medical interference (Figure 2). It appears that the major preventable factor is liaised with hypertension and its sequelae, or associated metabolic derangements.

Hypertension and dementia

Although hypertension has long been recognized to play a role in the pathogenesis of vascular dementia, its identification as an equipotent risk factor in

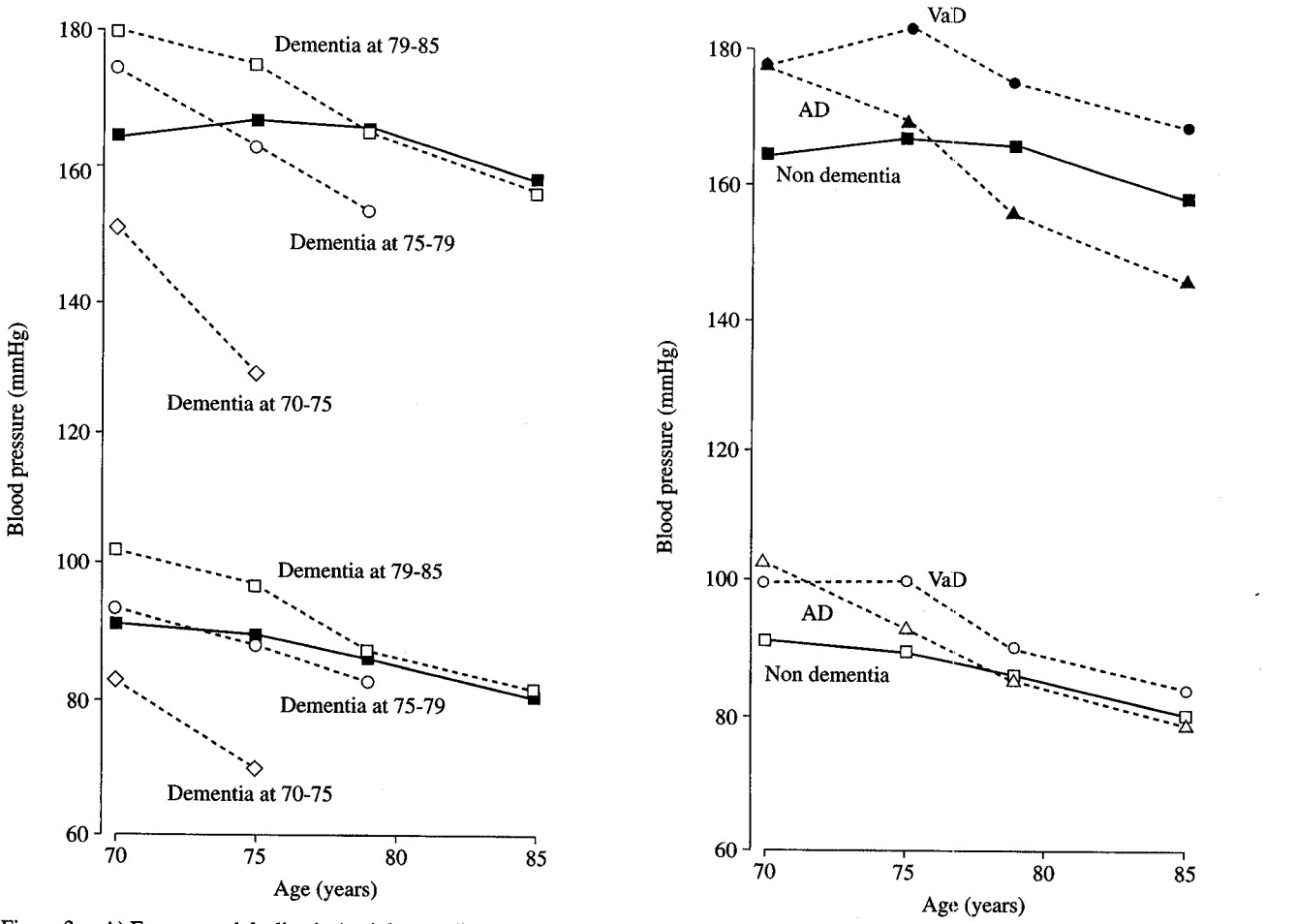

Figure 3.—A) Exaggerated decline in (mainly systolic) blood pressure in the years preceding the manifestation of Alzheimer's disease, in comparison with B) the course in non-demented subjects and those prone to develop vascular dementia. [Modified from Skoog *et al.*[18]].

Alzheimer's disease had to await the final decade of the past century. This has mainly been due to the lengthy lag phase between the clinical diagnoses of hypertension and cognitive deterioration, thus preventing consistent correlations between the two on a cross-sectional (contemporary) basis. The moot results of such comparisons have been extensively reported elsewhere.[13, 14] The extent of the apparent phase difference between the 2 conditions is due to the insidious nature of hypertensive target organ damage. For decades, histological lesions, such as neurofibrillary tangles, or an accelerated rate of neuronal atrophy in the medial temporal lobe of the brain,[15, 16] may precede overt dementia.

Since cross-sectional studies obviously lack the potency to disclose an *ad hoc* intimate relationship between blood pressure and cognitive deterioration, longitudinal studies were required to provide proper pro or contra evidence for a causative long-term relationship.

Over-all, such follow-up studies have revealed a high blood pressure to be a graded and continuous risk factor in the pathogenesis of both vascular and degenerative dementias in the course of the decade(s) following midlife.

In the Framingham study [17] blood pressure levels of participants aged 55-88 years were followed and averaged over 5 biennial examinations in an era (1956-1964) when the vast majority of hypertensives stayed untreated. In the period 1976-1978, in 1 038 untreat-

ed survivors the composite cognitive score with separate measures of attention and memory appeared to be inversely correlated with systolic and diastolic blood pressure at baseline.

The substance of this finding was confirmed in 2 studies from Sweden, Gothenburgh [18] and Uppsala [19] and by the Honolulu-Asia Study,[20] with follow-up periods of 15, 20 and 25 years, respectively.

While these studies basically established a positive relation between baseline blood pressure starting from midlife or over and the risk of cognitive impairment and overt dementia in the subsequent age range, this turned out to be less clear in subjects receiving antihypertensive treatment in the *interim*,[19] as could be expected.

A variant course of late-life events was discovered by Skoog's group in their meticulous follow-up of hypertensives aged 70 years and over.[18] They examined the relationship between blood pressure and dementia starting with non-demented patients at age 70 and following them at 5-year intervals up to age 85. In this observation period, patients prone to developing degenerative dementia later on had higher systolic and diastolic blood pressures than the others, but paradoxically exhibited a fall in blood pressure in the years before the onset of dementia (Figure 3).[18] White matter lesions on magnetic resonance imaging appeared to predispose to this phenomenon.[18]

This paradoxical decline in blood pressure in patients at increased risk of dementia is still to be explained. Physical inactivity in those blemished by advancing mental deterioration may be a substantial factor. Skoog proposed another hypothesis, in that failure to maintain usual blood pressure at this stage might well be an expression of Alzheimer-type lesions in prefrontal autonomic centres, resulting in central dysregulation of blood pressure control.[21] Orthostatic or postprandial dips in blood pressure, *pari passu* with episodes of impaired cerebrovascular blood flow might indeed contribute to further cerebrocellular damage.[22]

In this regard Belleli *et al.*[23] made an interesting and potentially relevant observation, in that increased 24 h blood pressure variability in elderly individuals appeared to be negatively correlated with the Mini-Mental State Examination score.

Whatever the mechanism of this rather ominous blood pressure decline, in practice it should require careful titration/adjustment of ongoing antihypertensive medication in the very elderly. The latter aspect will be discussed later on in this paper.

At the early part of the age spectrum another, recent observation regarded a comparable seemingly paradoxical development. Whilst it has been commonly accepted that the incidence of dementia exponentially increases with age with rates from 5 to 10 cases per 1 000 person-years at 70 years up to 20-40 cases at the age of 80,[10] it now seems that recognition of cognitive decline should no longer be limited to hypertension in the elderly. In the Maine-Syracuse Longitudinal Study of Hypertension Elias *et al.*[23] followed up subjects in 2 age groups (18-46 and 47-83 years) for (potentially) up to 20 years. In a sophisticated 2-step growth curve analysis, baseline blood pressures, categorized according to JNC VII [24] and various cognitive performance ratings were evaluated in both age groups. It appeared that the younger (in terms of a decline in visualization/fluid abilities) were equally vulnerable in relation to blood pressure increments as their older counterpart. This finding should serve as a perhaps even stronger stimulus to contain hypertension in its early stage than the avoidance of more distant mental sequelae.

Role of white matter lesions

White matter lesions on computed tomography (CT) or magnetic resonance imaging (MRI) are "endemic" among the elderly.[25] Still, their absence or presence may be clinically important, as already alluded to above in the study by Skoog *et al.*[18] The analysis/calibration of white matter lesions, particularly regarding cognitive impairment in vascular cerebral disorders, is being developed into a refined art [26] which may in due time hopefully be correlated with psychometric findings.

The role of hypertension in generating progressive white matter lesions, which correspond to ischemic destruction of deep neuronal axons, often with advanced microangiopathy (leading to focal infarcts as forerunners to stroke and/or neurodegenerative disorders), has long been ignored. This episode of ignorance/neglect has come to an end by virtue of a range of prospective cohort studies, where-in measurement of blood pressure at entry antedated magnetic resonance brain imaging by 5 to 20 years and was repeated at the time of the scans.

After adjustment for eventual confounders, the prevalence and incidence of white matter lesions augmented with high blood pressure.[27, 28] This pattern was sub-

sequently grosso modo confirmed by the CASCADE Consortium in which the above investigators closed ranks with those from 7 other European countries.[29] The association between white matter lesions and blood pressure was particularly strong in subjects with uncontrolled hypertension. It was graded and continuous for systolic pressure, but J-shaped for diastolic pressure. The Consortium speculated about various explanations that might underlie the latter aberrant relationship, but in our view they missed the most obvious angle.[29] With aging, systolic blood pressure tends to become the major cardiovascular risk factor. Contrariwise, a decline in diastolic blood pressure, in the same late course of aging reflects the same arteriosclerotic process as a marker of loss of arterial compliance in its own right. As a matter of fact, the cardiovascular risk of an increasing systolic blood pressure in the elderly has been shown to be proportionally reinforced by the presence of progressively reduced diastolic pressures.[30]

Observational studies on the effects of antihypertensive treatment on cognitive decline

Given the succesful effects of antihypertensive medication in containing stroke rates in elderly hypertensives [31-36] one could reasonably hope for analogous effects regarding the prevention of cognitive decline by protecting against cerebral microvascular damage as one of the substrate constituents of vascular, as well as degenerative, dementia.

A range of observational studies relating hypertension with cognitive malfunctioning incorporated the influence of concurrent antihypertensive medications.

In the Kungsholmen Project from Sweden,[31] 1 301 hypertensives aged 75 years and older were followed for an average of 3 years. Cognitive functions were assessed using the MMSE as well as additional psychometric criteria. At the end of the follow-up period 987 subjects were still alive. In a subpopulation with a systolic blood pressure higher than 160 mmHg, a diastoli blood pressure higher than 95 mmHg, or both, 122 had received diuretic treatment. Compared with untreated subjects, the patients thus treated showed an adjusted relative risk for developing dementia of 0.6 (C.I. 0.3-1.2). The authors felt that this outcome might indicate a potential benefit from diuretic treatment, although they recognized the flaws of this study, in that the information on treatment was merely available at baseline; moreover, confounding by indication may well have biased the results.

In a further follow-up phase of the Kungsholmen project,[32] it was observed that a very low diastolic blood pressure (<65 *versus* 66-90 mmHg) was associated with an increased risk for dementia, particularly in patients on antihypertensive treatment. Conversely, a high systolic blood pressure >180 mmHg carried a similar risk, whilst low systolic pressures (140 mmHg) appeared to be quite harmless. Apparently a further accumulation and integration of blood pressure data will be needed in order to arrive at a consensus for optimal blood pressure titration in terms of cognitive preservation.

In the Epidemiology of Vascular Aging Study (EVA),[33] 1 389 subjects, aged 59-74 years, were recruited, including 167 hypertensives who were re-examined 2 and 4 years later. After 4 years, 81 hypertensive individuals had received antihypertensive treatment with various drugs (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics, respectively). In untreated hypertensives a correlation was observed between the level of blood pressure and a subsequent decline in cognitive function (a decrement of >4 points on the 30 point MMSE scale). The relative risk amounted to 4.3 (95 C.I. 2.3-8) as compared with normotensives. By contrast, in the treated group of hypertensives the relative risk was reduced to 1.3 (C.I. 0.3-3.9).

Recently, a retrospective analysis has been published from Indiana, U.S.A.[34] This was based on centralized administrative data from 1 900 African Americans aged >65 years, without dementia at entry. They were followed up for a period of 5 years while being treated with a variety of 7 antihypertensive drugs. During that period, 288 individuals (15%) developed overt cognitive impairment. The use of antihypertensive medications over-all reduced the chance of developing dementia by 38% (odds ratio 0.62, 95% C.I. 0.48-0.84).

Although this looks encouraging, a corresponding analysis of reported blood pressure measurements was inconclusive. Moreover, none of the 7 antihypertensive drug categories prescribed, when evaluated separately, achieved significant reductions in odds ratios.

The above and further [35] results of antihypertensive treatment in reducing cognitive deterioration, although relatively encouraging in their own right, ought to be interpreted with skepticism because of their lack of

properly matched control groups and valid comparative statistics. Moreover, a precise relation between the antihypertensive effects of different drug types and the incidence rates of cognitive deterioration/overt dementia cannot be established. There also arise caveats regarding optimal levels of achieved blood pressures, both systolic and diastolic, in relation to aging, as witnessed by the follow-up study by Skoog *et al.*[18] In particular, a sharp decline in diastolic pressure in the elderly may well prove to be counterproductive, both in terms of systemic [30] and cerebral haemodynamic effects [32, 35, 36] as well as white matter lesions.[29]

A recent study from Beer Sheva (Israel) offers some further reasons for caution in that respect.[37] The latter authors studied 495 individuals (mean age 76.5 years) and related a range of cognitive functions to 4 groups of patients: untreated normotensives (n=136; average BP 122.6/72.6 mmHg); successfully treated (with calcium channel blockers or ACE-inhibitors) hypertensives (n=74; BP 126.8/74.5 mmHg); untreated hypertensives (n=103; BP 152/81 mmHg); and treated but so-called "uncontrolled" hypertensives (n=172; BP 158.7/85.4 mmHg).

Rather unexpectedly, the latter group scored best of all on the MMSE scale and in the cognitive domains of long term memory and concentration. The CCBs exhibited some additionally favorable action in this regard, an aspect which will be dealt with later on in this paper. The above results at first sight seem to deviate from current ideas about optimal (maximal) antihypertensive treatment. However these findings reinforce the relativism arising from quoted above,[18, 29, 30, 32, 35, 36] in that there may be a potential hazard of "overcorrecting" blood pressures in subjects aged 70 years and over. One does not need to be clairvoyant to realize that such utterly normalized blood pressure values as reported in the Beer Sheva study in elderly with long-standing hypertension may well interfere with their (chronically up-regulated) autoregulation of cerebral vascular resistance. Chronic underperfusion of the brain is quite likely to occur and thereby accentuate the process of cognitive decline.

Conversely, the provocative finding that non-responders to treatment performed better than untreated hypertensives is enigmatic and open to speculation (selective cerebral vasodilation? beneficial cerebrocellular effects?). We will return to the latter issue after discussing the literature on prospective randomized trials.

Results of long-term, prospective, randomized, placebo-controlled trials

In this regard, no specific trials have been conducted with a primary focus on prevention of cognitive deterioration per se. It stands to reason, that this kind of study had to be embedded in larger cardiovascular endpoint-oriented trials, if only for the obvious reason that mental disorientation cannot be studied in a somatic vacuum.

In the prospectively planned Medical Research Council trial of treatment in older patients with hypertension,[38] subjects were properly randomized to a diuretic, b-blocker, or placebo, respectively. Psychometric tests were performed covering a period of 54 months. In this substudy no significant differences in test scores were detected between the actively treated groups and those assigned to placebo. It should be noted, though, that there were numerous subjects from the placebo group crossing over to active treatment, which unavoidably has confused the results in terms of the "intention to treat" analysis applied to the above trial.

While the MRC study despite elaborate psychometric assessments unfortunately did not report on the incidence of overt dementia *per se*, other antihypertensive trials in the elderly focused on the incidence of dementia proper: SHEP,[39, 40] PROGRESS,[41] SCOPE,[42] Syst-Eur,[43] and Syst-Eur 2.[44]

In the Systolic Hypertension in the Elderly Program (SHEP) trial substudy on 2 034 subjects,[39] the incidence of dementia after 5 years was similar: in the placebo group 1.9% and in the group receiving treatment with chlorthalidone as the primary drug 1.6%. However, according to a later more detailed evaluation,[40] a differential drop-out and loss of data from participants in the placebo- and actively treated groups may well have biased the analysis of cognitive effects of active treatment and hence obscured a protective action of the antihypertensive regimen.

In the Perindopril Protection Protection against Recurrent Stroke Study (PROGRESS),[41] the ACE-inhibitor perindopril failed to prevent poststroke dementia. However, in combination with the diuretic indapamide a 23% reduction (p=0.05) in the incidence of dementia was observed.

The Study on Cognition and Prognosis in the Elderly (SCOPE),[42] tested the protective effect of the AT1-blocker candesartan against placebo. As to the latter group, it should be noted that 80% of patients on

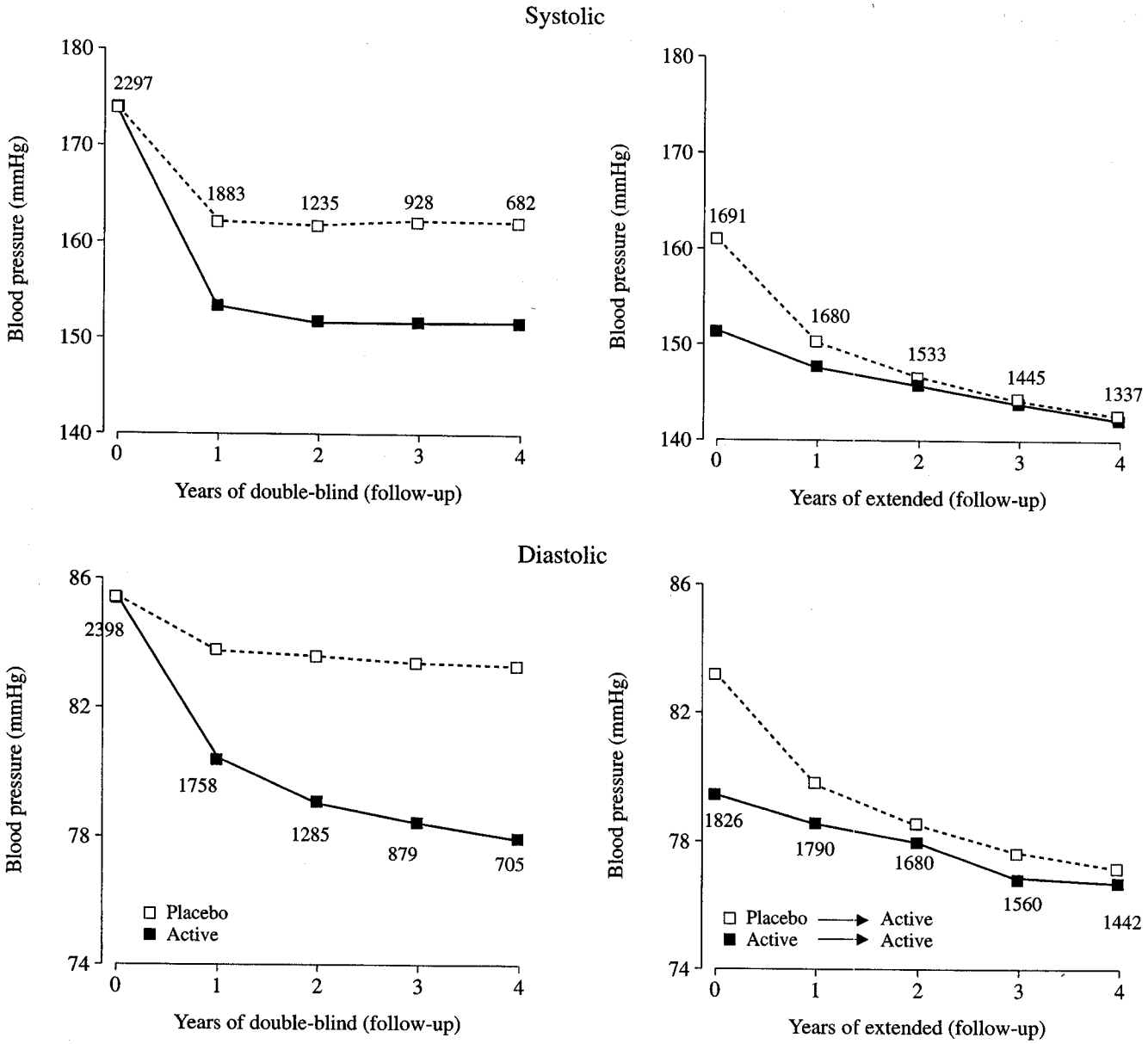

Figure 4.—Syst-Eur phases 1 and 2. Systolic and diastolic blood pressures in patients initially assigned to placebo or active treatment. Results are separately given for 4 695 patients randomized in the double-blind trial (A, C) and for 3 517 participants subsequently enrolled in the open label study (B, D). [From Staessen *et al.*[44]).

"placebo" actually received a diuretic for ethical reasons. Small wonder, that this procedure actually invalidated the trial results, which failed to demonstrate any protective effect of candesartan on dementia.

The Systolic Hypertension in Europe (Syst-Eur) trial included a side project investigating in a double-blind fashion the incidence of dementia in 2 418 subjects aged 60 years and over, with systolic hypertension.[43] The basic treatment consisted of the CCB nitrendipine vs matching placebo as primary drug, with enalapril and HCT and their matched placebos as complementary medication when considered to be

necessary. The median follow-up lasted only 2 years, because of a critical difference between stroke rates in the actively and placebo treated groups. Active treatment appeared to have reduced dementia by 50%, from 7.7 to 3.8 per 1 000 observation years in stroke-free subjects. After the close of the double-blind period it was decided for ethical reasons to offer all patients, including those in the former placebo group, the active form of trial medication for an extended period.

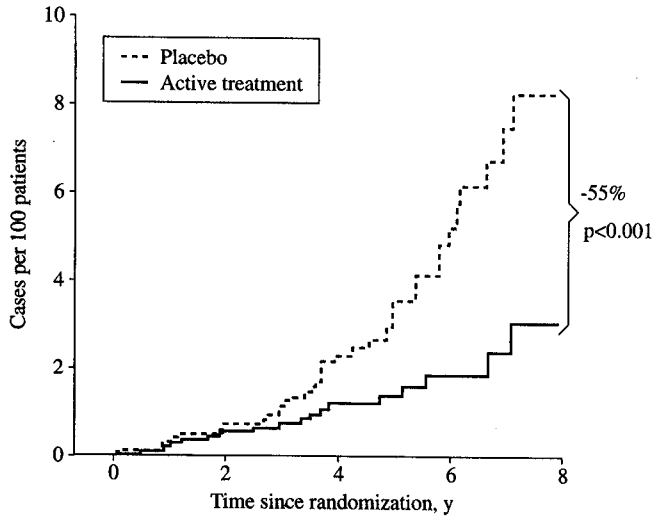

Figure 5.—Incidence of dementia in the Syst-Eur trial (double-blind phase followed by open active treatment phase ("intention to treat" mode of analysis). [From Forette *et al.*[45]].

This move, designated as Syst-Eur 2, doubled the observation period in an open fashion.[44]

As indicated in Figure 4,[44] in the course of the latter period blood pressures approached identity in the earlier placebo- and actively treated patients.[45] Nevertheless, the latter, as indicated in Figure 5,[45] still exhibited a relative profit in terms of avoiding or at least retarding the development of dementia (-55%, p<0.001).[45]

Altogether the combination of the above 4 trials would seem to offer only a slim profit of antihypertensive treatment in terms of preventing dementia: as indicated in Figure 6 [46] the over-all odds ratio was 0.89 (95% C.I. 0.75-1.04). Exclusion of drugs affecting the renin-angiotensin system (perindopril without indapamide, candesartan) would lead to a more promising pooled odds ratio: 0.75 (95% C.I. 0.60-0.94).[46] Despite its small numbers, the double-blind phase of

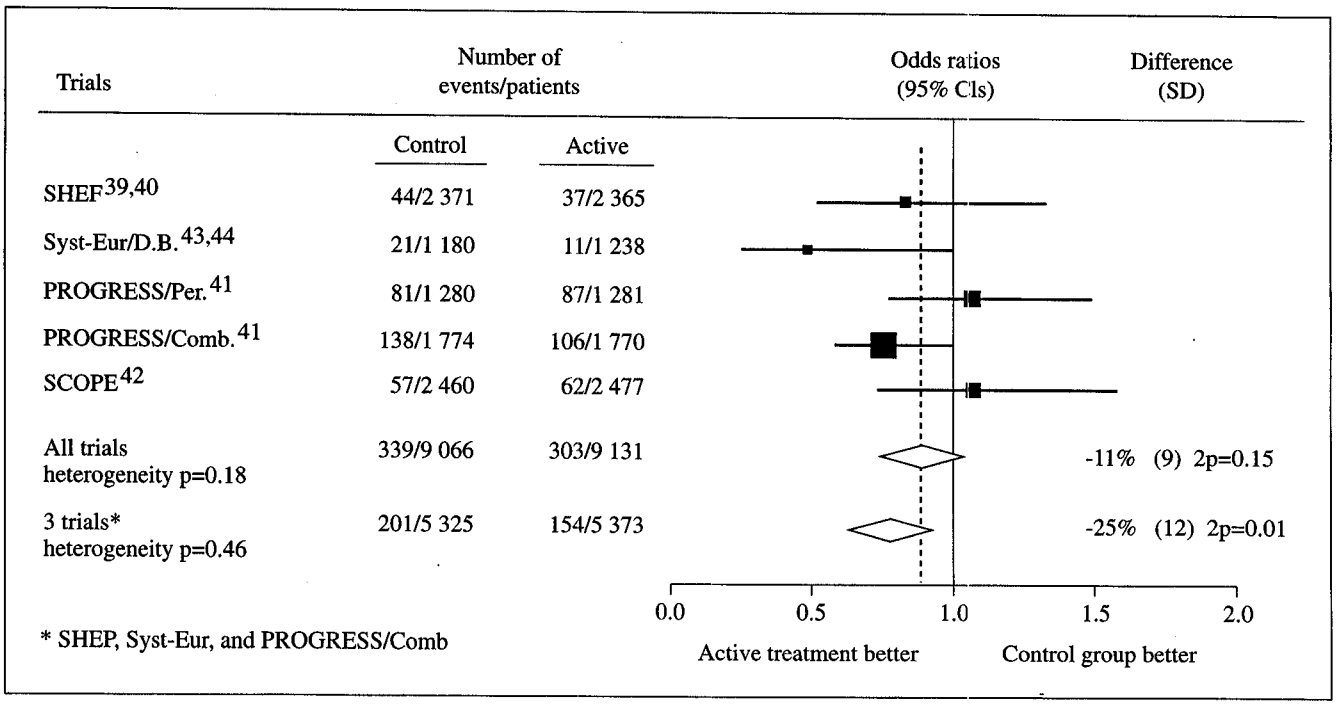

Figure 6.—Meta-analysis of randomized antihypertensive dementia prevention studies. [Based on Wang *et al.*46].

the Syst-Eur trial,[43] due to its primary drug nitrendipine, apparently carried the best message of preventing dementia (Figure 5).

Discussion and conclusions

Dementia (whether diagnosed as being of vascular or degenerative nature), due to increasing somatic longevity of the elderly population, looms ahead as an epidemic of catastrophic proportions. This will occur in the aging population at large, but apparently even more so in hypertensives. Whilst hypertensive target organ damage in general may be attenuated through adequate treatment with all currently available antihypertensive drugs, cognitive deterioration seems to be rather resistant to such routine treatment, as indicated above. This is (except for stroke-related dementia) presumably due to insidious hypertensive brain damage which apparently already has its roots at middle- or even younger age.

Our favourable experience in the Syst-Eur trial with the dihydropyridine calcium channel blocker as the primary drug is tempting us to recommend this class of antihypertensives for the prevention of both types of overt dementia, provided that the reduction in blood pressure remains within reasonable limits, for this age group, as indicated in Figure 4.

Some studies seemed to be at variance with our findings, but both were retrospective and confounded by indication, in the sense that CCBs were favoured for high risk patients.[47, 48] This is a particularly disturbing feature of the interpretation of treatment results of calcium blockers.[49]

A number of better organized, prospective studies (though not in a properly randomized, placebo-controlled fashion) respectively resulted in statistically significant favourable effects of the dihydropyridine CCB nimodipine on containing mental deterioration [50] and borderline significant protection by dihydropyridine CCBs as a drug class,[51] respectively.

From a conceptual point of view, this clinically-established capacity of dihydropyridine calcium channel blockers would be quite plausible. First of all, according to *in vitro* and *in vivo* experimental evidence intracellular free calcium accumulation plays a dominant role in age-related deterioration of a cascade of cerebrocellular functions, which are critically involved in brain aging, sensitization to neurotoxins, and cell death.[52-56] Secondly, the distribution of action of dihydropyridine CCBs (nitrendipine, nicardipine) has been shown to focus on areas in the rat brain corresponding to the human target cerebral areas involved in the development of dementias.[57, 58]

Since the circle of evidence regarding the efficacy of the dihydropyridine class of calcium antagonists in preventing/retarding the incidence of both types of dementia has virtually been closed, one can hardly forfeit the conclusion that such agents should at least be an ingredient of any hypertensive regimen for individuals aged >60 years, or perhaps even younger given recent findings.[23] We have argued repeatedly that there remains an urgent need for another long-term randomized comparative trial in hypertensives encompassing the current main classes of antihypertensive drugs, tailored to equal blood pressures and focusing on exponents of cognition.[14, 59] Unfortunately, the pharmaceutical industry turned out to be unresponsive to our detailed protocols, for whatever reason. It should therefore be conceived as a moral duty by the health authorities worldwide to become the patron of such an effort, with a view on preserving both somatic and mental health in the population at large as much as possible. The ALLHAT trial [60] could have fulfilled this purpose, if only the organizers would have monitored equal blood pressures more closely and planned proper attention to the course of cognitive aspects.

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